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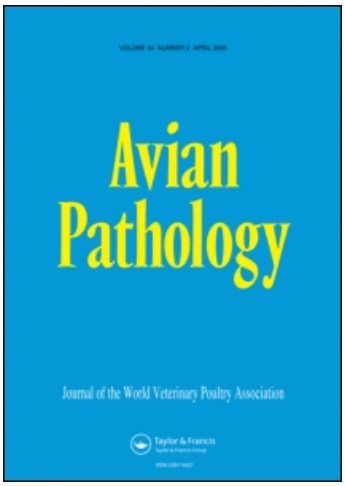

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REVIEW ARTICLE

The use of organic acids to combat *Salmonella* in poultry: a mechanistic explanation of the efficacy

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Salmonella is a human pathogen that is commonly found in poultry products. It is possible to decrease chicken carcass and egg contaminations by adding organic acids to the feed or drinking water at appropriate times. Medium-chain fatty acids are more antibacterial against *Salmonella* than short-chain fatty acids. The antibacterial effect of these acids is species specific. Bacteria that are unable to decrease intracellular pH accumulate organic acid anions in accordance with the pH gradient across their cell membranes. The short-chain fatty acid butyrate specifically down-regulates expression of invasion genes in *Salmonella* spp. at low doses. Also medium-chain fatty acids and propionate decrease the ability of *Salmonella* spp. to invade epithelial cells, in contrast to acetic acid. Because not all bacteria are affected in a similar fashion by organic acids, it may be possible to use probiotic and prebiotic bacteria to achieve beneficial effects. If diets can be designed to stimulate organic acid production in the caecum, it may be possible to control *Salmonella* spp. via even easier and more cost-effective measures, compared with addition of acids to feed or drinking water.

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Introduction

With the perception that antibiotics should no longer be used as animal growth promoters, there has been widespread interest in natural methods of inhibiting detrimental bacteria. Man has used fermentations as a method of food preservation for more than 6000 years (Ohmomo *et al.*, 2002), but now it appears that fermentation acids also have value as feed or drinking water additives. Commercial preparations appear to enhance digestibility and diet palatability, thus improving feed conversion and growth of animals, including pigs and poultry. Some acid mixtures prevent mould growth on feed, and claims of increased egg production have been made. Pathogen control has also been reported, but the peer-reviewed scientific literature has few definitive studies. Until recently, the use of short-chain fatty acids (SCFA), medium-chain fatty acids (MCFA) and other organic acids was largely based on their antimicrobial activity outside the intestinal tract. The present review describes the current use of organic acids to control *Salmonella* in poultry, attempts to provide a rationale for assessing potential pathogen control, summarizes *in vivo* experiments and field observations, and discusses future applications of using acids, bacteria or dietary changes to control *Salmonella*.

Bacterial Metabolism of Organic Acids

Bacteria can use organic acids as both carbon and energy sources. In *Escherichia coli*, the hydrophobic long-chain fatty acids (LCFA) ($\geq$C12) are transported across the cell membrane by carrier mechanisms, in which the fadL (outer membrane proteins) and the fadD proteins (inner membrane) are involved. FadL carries LCFA to the periplasmatic space and fadD is an acyl-CoA synthetase (Dirusso & Black, 2004; Van Den Berg, 2005). Once the acyl-CoA molecules are formed inside the cell, degradation occurs through the β-oxidation pathway, yielding multiple acetyl-CoA molecules (Clark & Cronan, 2005). Degradation of LCFA having an odd number of carbon atoms also yields propionyl-CoA as an end product. Whether MCFA (C6 to C10) can be transported by carrier proteins or are able to diffuse freely across the cell membrane in undissociated form is less clear, but also the fadD protein and the β-oxidation pathway are used for metabolization (Clark & Cronan, 2005). The LCFA and MCFA can also be used for incorporation in the membrane as phospholipids. SCFA ($\leq$C4) presumably cross the outer membrane mainly through diffusion in the undissociated form (Clark & Cronan, 2005). Once inside the cell, they can be converted to their CoA thioester forms. Butyric acid is converted to butyryl-CoA by the acetoacetyl-CoA transferase system (AtoAD system), converted to acetoacetyl-CoA by the fadB/E system, and then further breakdown to acetyl-CoA is performed by the atoB gene product (Jenkins & Nunn, 1987a,b; Clark & Cronan, 2005). Thus as an example, butyric acid is converted to two molecules of acetyl-CoA. Propionic acid, either

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taken up from the environment or generated as an end-product of degradation of LCFA with an odd number of carbon atoms is metabolized in *Salmonella* and *E. coli* in the methylcitrate cycle. Propionyl-CoA reacts with oxaloacetate to form 2-methylcitrate, which is converted through a series of reactions, mediated by the Prp operon, to succinate and pyruvate (Horswill & Escalante-Semerena, 1999). These products can be used in the citric acid cycle. Although it is thought that acetate can diffuse across the cell membrane, an acetate permease (ActP) was detected in *E. coli* (Gimenez *et al.*, 2003). In *E. coli* and *Salmonella*, acetate is converted to acetyl-CoA by either acetyl-CoA synthetase (encoded by the *acs* gene) or the sequential action of acetate kinase and phosphotransacetylase (encoded by ackA and pta, respectively) (Wolfe, 2005). Acetyl-CoA, generated by either the β-oxidation pathway, by butyric acid breakdown or by acetate conversion, can be used for oxidation in the citric acid cycle and for replenishing intermediates of the citric acid cycle via the glyoxylate shunt.

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Mechanism of Antimicrobial Activity of Organic Acids

Fermentative bacteria produce organic acids when oxygen is not available as a terminal electron acceptor, but they differ greatly in the types of acids that they produce. Because the oxidation of one molecule must be coupled to the reduction of another, anaerobic bacteria often produce several acids. The simplest fermentation is conversion of sugar to lactate, and many lactobacilli, streptococci, lactococci and enterococci have a scheme that is virtually homolactic when sugar is plentiful. However, when sugars are scarce, all of these bacteria are capable of switching to a fermentation that produces acetate, formate and ethanol, so ATP production can be enhanced. Butyric acid-producing bacteria typically utilize the hydrogenases of butyrate (or other even longer chain fatty acid) production as a mechanism of reducing equivalent disposal. If the bacterium has a hydrogenase, the interspecies hydrogen transfer to a methanogen decreases the need for dehydrogenase activity and acetate production typically is enhanced. Bacteria capable of utilizing fatty acids are found in stagnant anaerobic environments, but these bacteria grow very slowly, and fermentative environments are typically acidic. Fermentation acids are inhibitory when the pH is low but some bacteria are much more resistant than others.

Traditionally, microbial growth inhibition by organic acids was explained by the ability of these acids to pass across the cell membrane, dissociate in the more alkaline interior and acidify the cell cytoplasm (Kashket, 1987). Organic acids were compared with synthetic uncouplers that could remain membrane associated, and shuttle protons in a cyclic manner to dissipate the proton-motive force. The problem with this analogy is the fact that organic acid anions are charged and not lipid permeable. Indeed, the accumulation of benzoate anion is typically used to estimate intracellular pH. If benzoate acted like an uncoupler, the pH gradient across the cell membrane would be dissipated by the tool being used to measure it! The uncoupling model of fermentation acid toxicity also failed to address another practical question. Why are some bacteria so much more sensitive than others (Russell & Diez-Gonzalez, 1998)?

For many years it was assumed that bacteria maintained a slightly alkaline intracellular pH, but this assumption was largely based on work with laboratory cultures of *E. coli* (Padan *et al.*, 1981). It is now clear that many fermentative bacteria have the ability to let their intracellular pH decline when the extracellular pH becomes highly acidic. This decline in intracellular pH necessitates a metabolism that can tolerate a lower pH, but the strategy appears to be highly adaptive. When intracellular pH remains high, the pH gradient across the cell membrane can become very large. The protons can be pumped back out of the cell, but the pH gradient causes a logarithmic accumulation of the fermentation acid anions. By letting intracellular pH decrease, the bacterium has a much smaller pH gradient across the cell membrane and is protected from anion accumulation.

Continuous culture studies with *E. coli* K-12 and O157: H7 indicated that the two strains differed greatly in their sensitivity to acetate at pH 5.9, and the ability of O157: H7 to tolerate more acid than K-12 could be correlated with ability to decrease intracellular pH (Diez-Gonzalez & Russell, 1997). These experiments also revealed another important observation about fermentation acid toxicity. When the intracellular acetate concentration of K-12 increased, there was a nearly equal molar increase in intracellular potassium. These results indicated that fermentation acid anion accumulation was at least in part an osmotic stress. Recent work with *Clostridium sporogenes*, a silage and food contaminant, indicated that it accumulated lactate anion at acidic pH values in accordance with the pH gradient across the cell membrane, but lactate anion accumulation caused a secondary effect (Flythe & Russell, in press). When lactate anion increased, the cells lost intracellular glutamate, and the fermentation scheme of amino acid deamination is dependent on glutamate transaminase. The final result was a virtually complete inhibition of ammonia production. The antimicrobial activity of organic acids on other bacterial species has not been correlated with intracellular pH regulation, but bacteria that could be classified as neutrophils seem to be more sensitive than those that are acid tolerant. For example, the minimal inhibitory concentration (MIC) of acetic acid is 250 times lower for *Bacillus subtilis* than for lactobacilli (Hsiao & Siebert, 1999).

The anion model of organic acid toxicity explains why bacteria differ in their sensitivity to organic acids, but it does not provide information on the antibacterial effect of one acid versus another. The MIC values for acetic, butyric, lactic and caprylic acid in *E. coli* are less than 4 g/l, but this same bacterium is approximately 10 times more resistant to malic acid, tartaric acid and citric acid (Hsiao & Siebert, 1999). This observation indicates that factors such as chain length, side chain composition, p*K*a values and hydrophobicity could affect the antimicrobial activity.

Effects of Short-chain Fatty Acids on *Salmonella*

Antimicrobial activity against *Salmonella*. Less is known about the effect of organic acids on *Salmonella*, but it should be noted that *E. coli* and *Salmonella* are both enteric bacteria and seem to have a similar physiology. MCFA (C6 to C12; caproic acid, caprylic acid, capric acid and lauric acid) appear to be much more effective

against *Salmonella* than the SCFA (formic acid, acetic acid, propionic acid and butyric acid), but it is important to differentiate bactericidal and bacteriostatic effects. As little as 25 mM C6 to C10 acids were bacteriostatic to a *Salmonella* Enteritidis, but the same strain tolerated 100 mM SCFA (Van Immerseel *et al.*, 2003, 2004b). Sprong *et al.* (2001) reported that caprylic and capric acids were bactericidal, but C14:0, C18:1 and C18:2 acids were not. When *S.* Enteritidis and *Salmonella* Typhimurium were incubated with low concentrations of monocaprin (5 mM) that had been combined with an emulsifier, the bacteria did not survive (Thormar *et al.*, 2006). In general, these data indicate that MCFA have the greatest antibacterial activity against *Salmonella*, but large-scale studies are lacking.

Effect of Short-chain Fatty Acids on Virulence of *Salmonella*. *Salmonella* is an opportunistic intracellular pathogen that has an elaborate set of virulence genes. These genes enable the bacterium to adapt to the environment and move between various micro-niches within a host. An early step in the pathogenesis of *Salmonella* is the penetration of intestinal epithelium (Lostroh & Lee, 2001). This activity is promoted by invasion genes that are located on a pathogenicity island (SPI-1), but several pathogenicity islands are required for full virulence (Hensel, 2004). SPI-1 has genes encoding regulatory proteins, structural components of a needle complex and additional effector proteins. Bacterial effector proteins facilitate the entry of *Salmonella* into the cytosol of epithelial cells, by inducing actin rearrangements that lead to uptake of the bacteria. SPI-1 is in turn activated by HilA, and this latter protein is environmentally regulated. When *S.* Typhimurium was pre-incubated in growth media supplemented with various concentrations of butyrate and propionate, epithelial cell invasion was suppressed. However, if the cells were preincubated in media supplemented with acetate, invasion was still observed (Durant *et al.*, 1999; Lawhon *et al.*, 2002; Van Immerseel *et al.*, 2004a). Similar results were obtained with *S.* Enteritidis when primary caecal epithelial cells of the chicken were employed (Van Immerseel *et al.*, 2004a).

The effects of organic acids on epithelial invasion can be explained by changes in SPI-1 expression. Durant *et al.* (2000) measured *hilA* and *invF* (major activators of SPI-1) expression after exposure to acetate, butyrate and propionate in *S.* Typhimurium (2000). At pH 6, exposure of the bacteria to acetate increased the expression of these genes, but similar effects were not observed with propionate or butyrate. More recently, Lawhon *et al.* (2002) noted that butyrate and propionate, but not acetate, led to a decrease in *hilA*, *invF* and *sipC* expression. Acetate, after its conversion to acetyl-phosphate, acts to phosphorylate BarA and subsequently SirA. BarA/SirA is a two-component system thought to be involved in environmental sensing, and SirA enhanced transcription of *hilA*, finally resulting in increased invasion (Jones, 2005). DNA microarrays of both *S.* Typhimurium and *S.* Enteritidis indicated that low doses of butyric acid down-regulated SPI-1, but it did not alter metabolic gene expression. HilD, a positive regulator of HilA, was also down-regulated in both strains. *S.* Typhimurium and *S.* Enteritidis carrying plasmid-borne *hilA::luxCDABE* and *hilD::luxCDABE* transcriptional fusions confirmed the idea that butyrate down-regulated *hilA* and *hilD* (Gantois *et al.*, 2006). The primary target of butyrate in the bacterial cell is still unknown but butyrate could interfere with HilA-dependent regulation of SPI1 by altering the regulation of *hilD* transcription. These data indicate that SCFA can regulate the invasive phenotype of *Salmonella*, and it should be mentioned that pre-incubation of *Salmonella* with SCFA also increased acid resistance and survival in macrophages (Kwon & Ricke, 1998). Also, MCFA have been shown to decrease Salmonella invasion in intestinal epithelial cells (Van Immerseel et al., 2004b).

Effects of Short-chain Fatty Acids in *Salmonella* Control *in vivo*. The use of acidic compounds to control *Salmonella* first appeared in the late 1960s, and mainly focused on decontamination of carcass meal (Khan & Katamy, 1969; Smyser & Snoeyenbos, 1979; Van Staden *et al.*, 1980). Khan & Katamay (1969) evaluated the efficacy of 32 different acid preparations to decontaminate bone meal, and showed that low-molecular-weight volatile fatty acids were the most promising. Their results were a basis for the development of non-toxic, naturally occurring acidic compounds to control *Salmonella*. More than 35 years later, it is clear that their thoughts were prophetic. These acids have been added to feed, drinking water, and other matrices, in order to prevent *Salmonella* colonization of animal tissue and transmission through the food chain.

Poultry feed is a major source for *Salmonella* introduction to the farm (Williams, 1981). When chickens are given artificially contaminated feed, the gut is colonized and *Salmonella* are shed into the environment (Hinton, 1988). The original concept of incorporating acids into feed was based on the notion that the acids would decontaminate the feed itself and prevent *Salmonella* uptake by the chickens. When Iba & Berchieri (1995) inoculated feed with high doses of a *S.* Typhimurium strain, a commercial mixture of formic and propionic acid decreased the viability more than 1000-fold over 7 days. When broiler chicks were given the acid-treated feed that had been mixed with either *S.* Enteritidis, *S.* Typhimurium or Agona, the caecal *Salmonella* numbers were 7 $\log_{10}$ lower than control animals at day 5 (10^2 versus 10^9 colony-forming units (cfu)/g) (Iba & Berchieri, 1995). Mixtures of formic and propionic acid were also effective when feed was artificially inoculated with low doses of *Salmonella* Kedougou, and the decrease was most obvious after several weeks of storage (Hinton & Linton, 1988).

In a large-scale study (Humphrey & Lanning, 1988) the number of *Salmonella*-positive breeder feed samples decreased from 4.1 to 1.1% after the feed was supplemented with 0.5% formic acid. The antibacterial activities of organic acids was dependent on the temperature and moisture. Since the water content of poultry feed is generally low, the action of the acids is not always optimal, and it is not clear whether in-feed effects are the major reason for protection (Hinton, 1990). In the 1980s it became clear that the acid concentrations were also increased in the crop, and this antibacterial action could aid in controlling infection caused by horizontal transmission. Indeed, when the acid-treated feed is eaten by the chickens, it is both warmed and moistened and the activity of the SCFA should increase. It appears that supplemental acids are most apt to affect in the crop and gizzard rather than in the intestine. This point is

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illustrated in a study of Thompson & Hinton (1997), who fed laying hens a feed supplemented with a commercial mixture of formic and propionic acids. In these animals, pH values of the crop, gizzard, jejunum, caecum and colon were not altered relative to control animals, but formic acid and propionic acid concentrations in the crop and gizzard were significantly increased. At the same time, the lactic acid concentration in the crop decreased significantly, suggesting that lactobacilli were either inhibited or killed (Thompson & Hinton, 1997). This is in accordance with results obtained by Hume *et al.* (1993), in which large increases in propionic acid concentration in the crop of 4-day-old broilers were detected, when propionic acid was added to poultry feed, despite no observed changes in crop pH. Caecal SCFA patterns were not affected (Hume *et al.*, 1993).

Later in the 1980s, many studies examined the effects of supplemental acids on *Salmonella* colonization of chicken tissues. Actions of formic and propionic acids were variable. In a small-scale field trial, formic acid controlled shedding and caecal colonization by *Salmonella* serovars in naturally infected animals. Indeed, 50% of all control animals had *Salmonella*-positive cloacal swabs and caecal content samples, but *Salmonella* could not be detected in animals that consumed significant concentrations of formic acid (Hinton *et al.*, 1985). In a 3 year study, the cumulative number of infections of newly hatched chicks with *Salmonella* decreased after breeder stocks were given formic-acid-treated feed (Humphrey & Lanning, 1988). Breeders that received acidified feed had fewer numbers of *Salmonella* in the breeder litter (4.3 versus 1.4%), hatchery waste (15.3 versus 1.2%) and insert paper samples (4.6 versus 1.4%). These decreases were evident from the moment the breeders received acidified feed and illustrate the effects on vertical transmission (Humphrey & Lanning, 1988). The most striking proof of the efficacy of formic and propionic acids as feed additives to control *Salmonella* was given by Hinton & Linton (1988). In three independent experiments, no artificial infections or feed inoculations with *Salmonella* were performed. Formic acid-supplemented feed, given from the day of hatch, decreased the number of positive faeces and caecal content samples dramatically. The control groups had 25, 27 and 60% *Salmonella*-positive faecal samples, but the treatment groups had 3, 0 and 0% (Hinton & Linton, 1988). When the formic-acid-treated feed was given at a later age (16 or 32 days), no differences were detected between control and treated groups. This illustrates that preventing initial colonization of *Salmonella* is most important. Once an infection is established, it is very difficult to counteract using acid-treated feed, at least in the same production round.

When a formic acid and propionic acid mixture (0.5 to 0.68% w/w) was added to broiler feed that was artificially contaminated with very low numbers of *Salmonella* Kedougou (<50 cfu/g feed), only 1 of 30 groups (10 chickens each) became infected, compared with 22 out of 27 control groups (Hinton & Linton, 1988). These experiments were a basis for numerous publications on this topic. Izat *et al.* (1990a) found a significant effect when 0.4% propionic acid was added to broiler feed and the number of *Salmonella* bacteria on post-chill carcasses was assayed. No significant differences in *Salmonella* count in the small intestine could be detected, but the relevance of small intestinal sampling can be questioned because *Salmonella* mainly colonizes the caeca (Desmidt *et al.*, 1997). Izat *et al.* (1990b) concluded that formic acid addition to the feed was not a reliable means of reducing the incidence or level of *Salmonella* in the caeca or processed carcasses. Some reductions in caecal *Salmonella* were detected after calcium formate addition, but no effects were observed in most treatment groups (Izat *et al.*, 1990b). This can be attributed to the infection protocol. They infected the animals on days 2, 7, 14, 21 and 28 by adding *Salmonella* to the drinking water (approximately 10^5 per ml) rather than the feed. McHan & Shotts (1992) fed chickens a diet supplemented with 1% of a formic acid and propionic acid mixture and infected the animals at 2 days post-hatch with 10^6 cfu *S.* Typhimurium. They found significant reductions in caecal *Salmonella* colonization (>2.5 log units at 14 days of age, and >3.5 log units at 21 days of age). Hume *et al.* (1993) concluded that propionic acid (0.22%) in the feed was ineffective in reducing the number of *Salmonella* in the crop and caeca of broilers. There work was based on eight trials in which the broilers were inoculated with 10^4 cfu *S.* Typhimurium at day 4 of age, but they were sampled 6 days post-infection. The low dosage and the short time between infection and sampling could explain these results. When chickens received feed containing mixtures of formic acid and propionic acid, mortality after oral challenge with *Salmonella* Pullorum and *Salmonella* Gallinarum declined (Berchieri & Barrow, 1996; Al-Tarazi & Alshawabkeh, 2003).

Recently, researchers have attempted to transport the organic acids further down in the gastrointestinal tract by micro-encapsulation, which should prevent absorption of the acids in the upper tract and ensure release further down in the gastrointestinal tract. Van Immerseel *et al.* (2004c) examined the effect of microbeads containing formic acid, acetic acid, propionic acid and butyric acid on colonization of *S.* Enteritidis in the caeca, liver and spleen. Animals were infected (day 5 post-hatch) with $5x10^3$ cfu *S.* Enteritidis and samples were taken 3 days post-infection. Caecal colonization was significantly increased when acetic acid was added to the feed, but decreased when butyric acid was added. Internal organ colonization was increased if either formic acid or acetic acid were added to the feed, and this result is consistent with the idea that acids can enhance the virulence of *Salmonella* (see earlier). When powder and coated butyric acid additives (0.63 g/kg butyric acid) were compared using the same infection protocol, the coated form decreased colonization of the caeca but the powdered form did not (Van Immerseel *et al.*, 2005). The inability of the powdered form to give a positive response may have been due to the short time interval between infection and sampling. In an infection study using a seeder model in which 10 broilers were infected at day 5 post-hatch with 10^5 cfu *S.* Enteritidis and housed together with 40 non-inoculated broilers, 0.63 g/kg coated butyric acid in the feed significantly reduced shedding of *S.* Enteritidis in broilers until slaughter age. The effect of the acids on other members of the microbial community were not determined (Van Immerseel *et al.*, 2005).

Drinking water is a source for infection, so it is important to keep drinking water free of *Salmonella.* SCFA have also been used as drinking water sanitizers. In a study where "natural" infections were recorded,

Al-Chalaby *et al.* (1985) evaluated a commercial product containing propionic acid. The acids eliminated *Salmonella* in drinking water, while more than 80% of the samples in control groups were positive. This result could not be explained by *Salmonella* carriage because litter, cloacal swab and caecal content samples were not reduced (Al Chalaby *et al.*, 1985). Acetic acid, lactic acid or formic acid (0.5%) in drinking water reduced crop contamination after *S.* Typhimurium challenge (10^8 cfu) when feed had been withdrawn to simulate pre-transport conditions to the slaughter house (Byrd *et al.*, 2001). However, the number of positive caecal samples was not different between the treatment groups. Lactic acid and formic acid were even more effective than acetic acid. In a commercial farm study where broilers were provided 0.44% lactic acid in the drinking water during a 10 h feed withdrawal period, crop contamination and incidence of *Salmonella* in pre-chill carcass rinses were decreased (Byrd *et al.*, 2001). When moult was induced in layers by 9 days of feed removal and the animals were inoculated with *Salmonella* on day 4 of the feed withdrawal, neither acetic nor lactic acid (0.5%) significantly reduced crop or caecal colonization (Kubena *et al.*, 2005). These results seem to indicate that drinking water acidification is not as effective when chickens are moulted or highly stressed (Holt, 2003).

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Short-chain Fatty Acids in the Gut: A Key to Control Pathogen Colonization?

Feed and drinking water sanitation, and the addition of acid to the crop, appears to prevent pathogen colonization in the live animals, but the type of acid and its concentration can be very important. *Salmonella* colonization of the caeca and internal organs is not always affected by these treatments, especially if the infection pressure is high. Acids from feed or drinking water are not effective further down in the intestinal tract because *Salmonella* colonization is mainly in the caeca (Desmidt *et al.*, 1997). Because the caecum is the main fermentation site, the concentrations of SCFA are already higher there than in other intestinal segments (Engberg *et al.*, 2002). One-day-old broilers had no SCFA in their caeca, but concentrations were high by 10 days post-hatch (Van Der Wielen *et al.*, 2000). Acetic acid is the predominant short-chain fatty acid in the caeca, with concentrations ranging between 70 and 90 μmol/g caecal content (Engberg *et al.*, 2002; Van Der Wielen *et al.*, 2002). In most studies, the caecal butyrate concentration ranges between 10 and 40 μmol/g in chicken caeca, and the propionate concentration is even less (Engberg *et al.*, 2002; Van Der Wielen *et al.*, 2002). Because SCFA can affect invasion and virulence gene expression of *Salmonella* (Lawhon *et al.*, 2002; Van Immerseel *et al.*, 2004a; Gantois *et al.*, 2006), the natural quantities of the SCFA could play an important role in *Salmonella* colonization. If SCFA production in the caeca could be altered by changes in feed composition, producers would have a very cost-effective and efficient way of controlling *Salmonella*.

It has already been shown in various animal species that *Salmonella* colonization of the gut is decreased when the bifidobacterial population is increased, either by administration of bifidobacteria as probiotic strains or by addition of certain types of oligosaccharides that stimulation proliferation of these bacteria in the gut (Asahara *et al.*, 2001; Buddington *et al.*, 2002; Bovee-Oudenhoven *et al.*, 2003; Silva *et al.*, 2004; Thitaram *et al.*, 2005). When the caecal *Bifidobacterium* population in broilers was increased by isomalto-oligosaccharide addition to the feed, and the animals were infected with a high dose of *S.* Typhimurium, large reductions in caecal colonization were observed (Thitaram *et al.*, 2005).

Increases in lactic acid bacterial counts in the gut are correlated with increases in butyric acid concentrations (Kleessen *et al.*, 2001; Humblot *et al.*, 2005), and *Salmonella* colonization is decreased when butyric acid concentrations in the gut are increased (Van Immerseel *et al.*, 2004a, 2005). Bifidobacteria increase butyric acid concentrations, but these bacteria do not produce butyric acid themselves. Lactic acid bacteria, such as lactobacilli and bifidobacteria, stimulate proliferation of butyric-acid-producing bacteria. This mechanism is called cross-feeding. It has been shown that lactic acid, produced *in vitro* by *Bifidobacterium adolescentis* with starch as the sole carbon source, is used by *Anaerostipes caccae* and *Eubacterium hallii* (in co-culture) for the production of large concentrations of butyric acid (Duncan *et al.*, 2004). Another approach would be a direct stimulation of butyric-acid-producing bacteria. In human gut samples, butyric acid producers are anaerobic bacteria belonging to the phylogenetic Clostridium clusters IV and XIVa (Pryde *et al.*, 2002), and species related to *Roseburia*, *Eubacterium*, *Faecalibacterium* and *Coprococcus* can also produce butyrate (Pryde *et al.*, 2002). Many of the butyrate-producing microbiota that are identified are net consumers of acetate (Duncan *et al.*, 2004). It is not clear whether similar mechanisms exist in poultry gut microbiota. Random cloning and sequencing of 16S rDNA sequences isolated from chicken caeca revealed more than 85% of the clones belonging to eubacteria and clostridia (Bjerrum, 2005). Approximately 10% of the clones had high similarity with *Faecalibacterium prausnitzii*, a species that produces butyric acid in the human gut (Bjerrum, 2005).

Concluding Remarks

It is now evident that the addition of organic acids can have a beneficial effect on the quality of poultry by decreasing *Salmonella* and possibly other potentially pathogenic bacteria. The idea that probiotic and prebiotic applications, or simply rational design of feed composition, could lead to similar effects producing favourable SCFA patterns is an interesting hypothesis, but research on this matter in poultry is still lacking. Recent studies have just started to generally describe the caecal microbiota of chickens (Lu *et al.*, 2003; Bjerrum, 2005).

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REVIEW ARTICLE
Non-English Abstracts

The use of organic acids to combat *Salmonella* in poultry: a mechanistic explanation of the efficacy

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Utilisation d'acides organiques pour combattre les salmonelles chez les volailles: mécanisme d'efficacité
Les salmonelles sont, pour l'homme, des agents pathogènes qui se retrouvent communément dans les produits avicoles. Il est possible de diminuer les contaminations des carcasses de poulet et des æufs en ajoutant des acides organiques aux aliments ou à l'eau de boisson à des moments appropriés. Les acides gras à chaîne moyenne sont plus antibactériens contre les salmonelles que les acides gras à chaîne courte. L'effet antibactérien de ces acides est spécifique d'espèce. Les bactéries qui ne sont pas capables de diminuer le pH intracellulaire accumulent les anions d'acides organiques suivant le gradient de pH au travers de leurs membranes cellulaires. Le butyrate, acide gras à chaîne courte, diminue spécifiquement l'expression des gènes d'invasion chez *Salmonella* spp., à doses faibles. De même, les acides gras à chaîne moyenne et le propionate diminuent la capacité de *Salmonella* spp. d'envahir les cellules épithéliales, contrairement à l'acide acétique. Du fait que toutes les bactéries ne sont pas affectées de la même façon par les acides organiques, il peut être possible d'utiliser des probiotiques et des prébiotiques pour atteindre des effets bénéfiques. Si des régimes alimentaires peuvent être définis pour stimuler la production d'acides organiques dans les cæca, il peut être possible de contrôler *Salmonella* spp. de façon encore plus facile et plus rentable, par rapport à l'addition d'acides dans l'aliment ou dans l'eau de boisson.

Die Verwendung von organischen Säuren zur Bekämpfung von Salmonellen beim Geflügel: Erklärung des Wirkungsmechanismus
Salmonellen sind humane Infektionserreger, die häufig in Geflügelprodukten gefunden werden. Durch die Zugabe von organischen Säuren zum Futter oder Trinkwasser zum richtigen Zeitpunkt ist es möglich, die Kontamination von Hühnerschlachtkörpern und -eiern zu verringern. Mittellangkettige Fettsäuren besitzen eine stärkere antibakterielle Wirkung gegen *Salmonella* als kurzkettige Fettsäuren. Der antibakterielle Effekt dieser Säuren ist speziesspezifisch. Bakterien, die nicht in der Lage sind, den intrazellulären pH zu senken, akkumulieren organische Säureanionen entsprechend dem pH-Gradienten über ihre Zellmembranen. Speziell die kurzkettige Buttersäure reguliert die Exprimierung von Invasionsgenen von *Salmonella* spp. in geringen Dosen runter. Auch mittellangkettige Fettsäuren und Proprionatsäure verringern im Gegensatz zu Essigsäure die Fähigkeit von *Salmonella* spp. in Epithelzellen einzudringen. Da nicht alle Bakterien in gleicher Weise von organischen Säuren beeinflusst werden, kann der Einsatz von pro- und präbiotischen Bakterien eine positive Auswirkung haben. Wenn Diäten zusammengesetzt werden können, um die Bildung von organischen Säuren im Zäkum zu stimulieren, wird im Vergleich mit dem Zusatz von Säuren zu Futter oder Trinkwasser sogar eine leichtere und kostengünstigere Salmonellenbekämpfung möglich sein.

El uso de ácidos orgánicos para combatir frente a Salmonella en avicultura: una explicación mecánica de su eficacia
Salmonella es un patógeno humano que se aísla frecuentemente en productos avícolas. Es posible reducir la contaminación de las canales y huevos mediante la adición de ácidos orgánicos en el pienso o en el agua de bebida en momentos apropiados. Los ácidos grasos de cadena media tienen mayor efecto antibacteriano

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frente a *Salmonella* que los ácidos grasos de cadena corta. El efecto antibacteriano de estos ácidos es especie-específico. Aquellas bacterias que son incapaces de reducir el pH intracelular acumulan aniones de ácidos orgánicos en función del gradiente de pH a través de sus membranas celulares. El butirato, ácido graso de cadena corta, regula específicamente a la baja la expresión de genes invasivos en *Salmonella* spp. a dosis bajas. También otros ácidos grasos de cadena media y los propionatos reducen la capacidad de *Salmonella* spp. de invadir células epiteliales, en comparación con el ácido acético. El uso de bacterias como prebióticos y probióticos para obtener efectos beneficiosos es posible debido a que los ácidos orgánicos no las afectan por igual. Así pues si pudieran diseñarse dietas para estimular la producción de ácidos grasos en el ciego, se lograría el control de *Salmonella* spp. mediante medidas sencillas y con mejor relación coste-eficacia, en comparación con la adición de ácidos al pienso o al agua de bebida.

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